EVIDENCE ON THE DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF BROMACIL LITHIUM SALT

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Bromacil Lithium Salt

- Herbicide (MW 267 D)
  Used primarily on rights-of-way
- Commercial preparation by dissolving bromacil in solution of lithium hydroxide (LiOH)
- Bromacil is weak organic acid, mass of 261 D.
  Forms ion with valence of -1
- Lithium is an alkali metal, mass of 6.94 D. Forms ion with valence of +1
- Bromacil lithium salt preparation must be at least 1 mole lithium per mole bromacil.

Pharmacokinetics: bromacil

- Bromacil rapidly absorbed orally
- Hydroxylated at side-chains
- Widely distributed in body
- Excreted in urine
- Does not accumulate

Pharmacokinetics: lithium

- Lithium rapidly absorbed orally
- Not metabolized
- Widely distributed in body: distributes to fetus
- Excreted in urine and sweat
- Does not accumulate

Acute oral and inhalation LD_{50}s in rats (mmol/kg).

Compound	Bromacil		Bromacil Li		Li (Cl)
Strain	Sprague Dawley	Sprague Dawley	Sprague Dawley	Sprague Dawley	Wistar
Sex	Male	Female	Male	Female	Male
Oral gavage	6.1	4.0	3.2	1.2	12.4-19.8
Inhalation (4 hr.)	> 2.7	> 2.8	> 0.76	0.62	NR

Non-DART toxicities: bromacil

- Rats and dogs: reduced food intake, body weight, weight gain.
- Mice: adverse effects on immune system organs, pancreas, liver, kidney, lung.

Non-DART toxicities: lithium

- Humans (mild): drowsiness, fine hand tremor, increased water consumption and urine output, effects on thyroid
  Humans (severe): nausea, vomiting, diarrhea, tremor, sedation or confusion, ataxia, nystagmus, coma, convulsions. Death.
  - Has a very narrow therapeutic index

- Animals: reduced food consumption, weight loss, drowsiness leading to stupor.
  When administered in water, reduced water consumption.
  When administered by gavage or food, increased water consumption and urine output.
  Death.

Developmental toxicity studies of bromacil and lithuim

- Bromacil lithium salt:
  no human or animal studies
- Bromacil:
  animal studies
- Lithium:
  human and animal studies

Developmental effects with bromacil in animals by oral and inhalation routes

Studies:

- Rat and rabbit developmental
- Rat reproductive

Effects observed:

- Retarded development (reduced fetal weight in rat by inhalation at 0.007, 0.014, 0.030 mmol/kg/d, skeletal retardation in rat by gavage at 1.9 mmol/kg/d)
- Skeletal variations (rat by gavage at 0.77, 1.9 mmol/kg/d, rabbit by gavage at 1.9 mmol/kg/d)

Human studies with lithium of developmental outcomes

Schou 1973	Retrospective	cardiac malformations Ebstein's anomaly
Weinstein & Goldfield 1975	Retrospective	cardiac malformations Ebstein's anomaly
Kallen & Tandberg 1983	Cohort	malformations cardiac defects neonatal deaths
Schou 1990	Retrospective	malformations cardiac defects Ebstein's anomaly

Human studies with lithium of developmental outcomes cont.

Zalstein et al. 1990	Case Control	No effect
Czeizel and Racz, 1990	Case Control	No effect
Jacobson et al., 1992	Prospective	No effect
Troyer et al., 1993	Cohort	Premature delivery

Possible explanations for inconsistency of lithium human study results

- Different study designs
- Varying power to detect an association
- Difficulties in assessing outcome of concern (Ebstein's anomaly)
- Lack of quantitative exposure assessment
  -- lithium dosage (varying levels of exposure)
  -- serum lithium levels
    - o rapid vs. slow release formulations
    - o anti-inflammatory drugs

Developmental effects with lithium in animals by oral routes

Studies:

- Mice, rats, rabbits, monkeys

Effects observed:

- Death of embryo, fetus, or neonate (mice and rats)
- Malformations (e.g. cleft palate, long bones defects) (mice and rats)
- Growth retardation (e.g. fetal weight) (mice and rats)

Note: no evidence for heart defects

Developmental effects with lithium in animals by injection routes

Studies:

- Mice, rats

Effects observed:

- Death of embryo or fetus (mice and rats)
- Malformations (e.g. exencephaly) (mice and rats)
- Growth retardation (e.g. fetal weight) (mice)

Note: no evidence for heart defects

Consistency of results between animal studies with lithium

- Difficult to assess consistency due to differing study designs
- Many differences in results can be attributed to dose-response
- Other factors involved: species, strain, route, duration, endpoints reported

Comparison of rat developmental studies by gavage using lithium or bromacil

Ref.	Chemical	Strain	Time	DART	**NOEL**, LOEL, EL (mmol/kg/d)
Alvarez (1988)	Bromacil	SD	Gd 7-16	Skeletal variations and retardation	**0.29**, 0.77, 1.9
Marathe & Thomas 1986	Lithium	Wistar	Gd 6-15	Resorptions, litter size, malformations, fetal weight	**1.35**, 2.7
Fritz (1988)	Lithium	SD	Gd 16-20	Embryonic & fetal death, live litter size, fetal weight	2.7
Fritz (1988)	Lithium	SD	Gd 16-20	Pnd 1 litter size	1.6

Female reproductive toxicity studies of bromacil and lithuim

- Bromacil lithium salt:
  no human or animal studies
- Bromacil:
  animal studies
- Lithium:
  human and animal studies

Female reproductive effects with bromacil in animals by oral routes

Studies:

- Rat reproductive
- Rat, mouse, and dog chronic

Effects observed:

- No adverse female reproductive effects

Human studies with lithium of female reproductive outcomes

Baptista et al., 2002	Prospective	No change in female reproductive hormone levels or menstruation (elevated TSH)
Ghadirian et al., 1992	Retrospective	No association between lithium treatment alone and sexual function.
Kristensen and Jorgensen, 1987	Retrospective	No association between lithium treatment and sexual dysfunction.

Female reproductive effects with lithium in animals by oral routes

Studies:

- Rats, mice

Effects observed:

- Reduced fertility (mice: both M and F treated at 50 or 100 mmol Li/L water, rats: 25 mmol Li/L water)
- Reduced litter size (rats: 20 mmol Li/L water, 2 gens, and 15 mmol Li/L water)
- Reduced corpora lutea, implantations (rats: 20 mmol Li/L water)
- Cessation of estrus cycling (mice: 94 mmol Li/kg food)
- Aberrant parenting behavior (rats: 2-4 mmol/kg/d in water)

Female reproductive effects with lithium in animals by injection routes

Studies:

- Mice and rats

Effects observed:

- Altered female reproductive hormones (mice and rats)
- Reduced ovary & uterus weight (rats)
- Increased length of estrus cycles (rats)
- Aberrant parenting (rats)

Male reproductive toxicity studies of bromacil and lithuim

- Bromacil lithium salt:
  no human or animal studies
- Bromacil:
  animal studies
- Lithium:
  human and animal studies

Male reproductive effects with bromacil in animals by oral routes

Studies:

- Rat reproductive
- Mouse, rat, and dog chronic

Effects observed:

- Increased incidence of testicular tubule atrophy (mouse: food at 0.15, 0.75, 3.3 mmol bromacil/kg/d, not in rat or dog)

Human studies with lithium of male reproductive effects

Sperm parameters:

- Clinical studies
- Reduced sperm viability in 2 reports (1 study?)
- No effect in 1 study

- In vitro studies
- Reduced sperm motility in 3 studies (EC_{50} 6-25 mM)
- No effect 1 study

Human studies with lithium of male reproductive effects cont.

Plasma sex hormones:

- Testosterone below normal in 7/10 patients in 1 study
- No effect on testosterone, increased LH in 1 study

Sexual function:

- Case report of loss of libido (2 patients)
- No association of sexual dysfunction with lithium use in 3 studies

Male reproductive effects with lithium in animals by oral routes

Studies:

- Mice and rats

Effects observed:

- Reduced fertility (mice: both M and F treated at 50 or 100 mmol Li/L water, not rats)
- Reduced plasma testosterone (mice: 94 mmol Li/kg in food, rats: 15 mmol Li/L water)

Male reproductive effects with lithium in animals by injection routes

Studies:

- Mice, rats, viscacha

Effects observed:

- Reduced testosterone, alterations to other male reproductive hormones (dependent upon specifics of administration) (rats)
- Reduced testes and other male reproductive organ weights (rats)
- Reduced numbers of spermatogonia and spermatids (rats)
- Increased testosterone 1 study (mice)

Summary: developmental bromacil

Effects observed:

- Retarded development and skeletal variations in developmental studies in rats and rabbits

Summary: Developmental lithium

Human effects observed:

- Malformations (especially cardiac) in earlier studies
- Neonatal death
- Premature delivery

Summary: Developmental lithium cont.

Animal effects by oral routes:

- Death, malformations, retarded development in rats and mice

Animal effects by injection routes:

- Death, malformations, retarded development

Summary: female reproductive bromacil

- No adverse effects observed

Summary: female reproductive lithium

Human:

- No association of lithium use with altered female reproductive hormones, menstruation, or sexual function

Summary: female reproductive lithium cont.

Animal effects by oral routes:

- Reduced fertility, litter size, corpora lutea
- Cessation of estrus cycling
- Aberrant parenting behavior

Animal effects by injection routes:

- Altered female reproductive hormones
- Reduced ovary & uterus weights
- Increased length of estrus cycles
- Aberrant parenting behavior

Summary: male reproductive bromacil

Effects observed:

- Testicular atrophy in mice (chronic study)

Summary: male reproductive lithium

Human:

- Reduced sperm viability
- Reduced testosterone
- Reduced libido

Summary: male reproductive lithium cont.

Animal effects by oral routes:

- Reduced fertility (?)
- Reduced testosterone

Animal effects by injection routes:

- Reduced testosterone, other male repro hormones altered
- Reduced testes, other male repro organ weights
- Reduced numbers of spermatagonia and spermatids